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Item No.: 6064

Responses to Public Comments on the Office of Pesticide Program's Draft Science Policy Documents:

Data for Refining Anticipated Residue Estimates Used in Dietary Risk Assessments

Guidelines for the Conduct of Bridging Studies for Use in Probabilistic Risk Assessment

Guidelines for the Conduct of Residue Decline Studies for Use in Probabilistic Risk Assessment

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June 15, 2000

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List of Acronyms

AR	Anticipated Residue
BDL	Below Detection Limit
BQL	Below Quantification Limit
CEC	Critical Exposure Contributor
CFR	Code of Federal Regulations
CSFII	Continuing Survey of Food Intake by Individuals
DEEM™	Dietary Exposure Evaluation Model
EPA	U.S. Environmental Protection Agency
FARAD	Food Analysis Residue Avoidance Databank
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FR	Federal Register
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	The Food Quality Protection Act of 1996
FSIS	Food Safety Inspection Service
HAFT	Highest Average Field Trial
HED	The Health Effects Division of the Office of Pesticide Programs
IWG	Implementation Working Group
LOD	Limit of Detection
LOF	"Lack of Fit"
LOQ	Limit of Quantification
MaxLIP	Maximum Likelihood Imputation Procedure
ND	Nondetects or nondetectable
OP	Organophosphate
OPP	Office of Pesticide Programs
OPPTS	U.S. EPA's Office of Prevention, Pesticides, and Toxic Substances
PCT	Percent of Crop Treated
PDP	Pesticide Data Program
PHI	Preharvest Interval
RAC	Raw Agricultural Commodity
SAP	FIFRA Scientific Advisory Panel
SOP	Standard Operating Procedure
TRAC	Tolerance Reassessment Advisory Committee
USDA	U.S. Department of Agriculture

I. INTRODUCTION

A. Background

On April 7, 1999 the U.S. Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP) issued in the *Federal Register* (64 FR 16967) a Notice of Availability (along with a request for comment) for a science policy paper entitled "Data for Refining Anticipated Residue Estimates Used in Dietary Risk Assessments for Organophosphate Pesticides," (EPA 1999a) hereafter referred to as the "AR (anticipated residue) paper." This document described the types of data that can be used to refine residue estimates for dietary exposure assessments. The purpose of the paper was two-fold: (1) to explain when and how EPA could use these types of data; and (2) to determine the extent to which such data were already available. After reviewing the comments and information received in response to the AR paper (submitted under docket OPP-00591), OPP drafted specific guidelines for conducting bridging and residue decline studies. These two subsequent guidance documents were also made available for public comment through a notice in the *Federal Register* (64 FR 42372) on August 4, 1999 (EPA 1999b; 1999c).

A total of 14 comments were received on the AR paper (submitted under docket OPP-00591); six comments were received on the bridging and residue decline study guidance (submitted under docket OPP-00616). Because these papers and the comments received are very closely related, OPP has chosen to respond to the comments on all three papers in this one document. Commenters included pesticide registrants, environmental and public interest groups, consultants, private citizens, professionals affiliated with land-grant universities, and the FQPA Implementation Working Group (IWG), as well as numerous individual state farm bureaus that support the IWG. All comments and recommendations were reviewed by OPP and incorporated, as appropriate, into one revised science policy document. A listing of the names and affiliations of the parties submitting comments is provided at the end of this document (see Section IV– List of Commenters).

B. Organization of this Document

This document contains OPP's responses to the comments raised on three draft science policy papers. The document is organized by topic area, each of which contains a brief summary of the relevant sections of the draft science policies, a synopsis of the public comments that were submitted, and the Agency's response. These responses include discussion of the comments received on specific questions posed by OPP in each of the science policy papers. The specific questions posed in the AR paper were:

- EPA proposes to: review existing bridging, residue decline, and other data; and develop guidance for conducting these kinds of studies. The purpose of these multi-rate, multi-preharvest interval (PHI) studies is to be able to use the full range of expected residue values (based on the full range of application rates and PHI's) in dietary exposure assessments and thereby produce more realistic estimates of dietary risk. Is this a reasonable and efficient approach? What other approaches should EPA consider?

- EPA believes that between one and three field trials conducted at different locations (with three different application rates at each field trial and three independent samples collected at each rate or PHI) are needed to demonstrate the mathematical relationship between application rate or PHI and amount of residue. Is this sampling regime adequate to characterize the range of potential residues?

- In developing its guidance, EPA has assumed that the relationship between application rates and/or PHI's and resulting residue levels is not necessarily the same for all chemicals. Is there any information available to suggest that this assumption is incorrect? Is there any information available to suggest that the relationship between application rates and/or PHI's and resulting residue levels for the organophosphates (OP's) as a class may be similar?

- EPA is willing to consider data on the prevalence of food processing practices, along with data to quantify residue reductions from such practices. Should information on the extent of food processing practices be validated? If so, how could this be accomplished?

Due to the similarity in the methods and techniques of the companion papers presenting draft guidance for conducting bridging and residue decline studies, EPA posed the same questions for each of these documents, as follows:

- Is the guidance provided in these draft documents clear and complete? If not, why not and what additional guidance is needed?

- Are the residue studies described in these documents adequate for generating refined acute dietary probabilistic exposure and risk assessments? If not, why not and how should they be modified?

- OPP has proposed that between one and three field trials be conducted, that at least three application rates and/or five PHI's be tested, and that three composite samples be collected at each application rate or PHI. Do these recommendations appear to be reasonable and sufficient to establish a rate *vs.* residue or PHI *vs*. residue relationship? Are data available that indicate that these guidelines are adequate for the purposes intended? Explain.

- OPP has stated that it believes that the field trials performed for bridging study/residue decline purposes should be conducted at an exaggerated rate, if necessary, such that all residues are "quantifiable" (*i.e*., at or greater than the LOQ). We have stated that it would be considered inappropriate to derive a quantitative relationship between application rate and residue level on residues that are below the LOQ as this could introduce substantial uncertainty into the estimated relationship. Please comment on this proposed restriction. Please also comment on the recommendation that studies be conducted at an exaggerated rate, if necessary, to avoid the potential problem associated with nondetectable (ND) residues.

- OPP states that extrapolation of data between similar crops may be allowed on a case-by-case basis considering similar cultural practices and application patterns. Should these extrapolations be limited to crops within a crop subgroup/group or should more extensive extrapolations between groups be permitted? If so, on what basis should more extensive extrapolations be permitted?

- For the relationship produced by bridging or residue decline data to be used in an exposure assessment, it is necessary to have reliable usage data concerning application rates and/or PHI's. For example, if residues resulting from the full (maximum) application rate, three-quarters of the maximum application rate, and one-half the maximum application are determined, it is necessary to also have information on the percentage (or fraction) of the time each of these application rates are used. A similar situation exists for PHI's. Is this information available from either public or proprietary sources? If so, from which sources can these data be obtained and how readily available are they?

- The proposed methodology uses what is believed to be the statistically more appropriate "lack of fit" (LOF) test to determine if the hypothesized model (*e.g.*, linear relationship between application rate and residue level, first order decay in residue concentration with time, *etc*.) is adequate to describe the data. Please comment on this proposed approach and compare it with the more widely used coefficient of determination (r^2). Under what circumstances might the use of r^2 to judge a fit adequate be preferred to the "lack of fit" test? Should the two be used in conjunction with one another and if so, how? There may be instances where the "lack of fit" test reveals that the hypothesized linear association can be rejected, but the coefficient of determination shows that the linear relationship accounts for a significant portion of the variability. What statistical tests, if any, should be used to judge whether the r^2 is significant?

- OPP will require that *composite* samples be collected as part of reduced-use field trials to retain comparability with earlier maximum rate/minimum PHI field trials conducted to support tolerance decisions. Nevertheless, OPP still has concerns about the effect compositing may have on unit-to-unit variation. When residue estimates are generated from maximum application rate and minimum PHI's (worst case conditions), OPP believes that there is an adequate degree of compensating overestimation such that individual unit variation is not of concern. By incorporating the range of application rates and PHI's in a probabilistic scenario, the conservatism built into EPA's use of field trial data is eroded and may require the Agency to compensate for this with statistically valid data on individual samples and/or unit-to-unit variation. OPP is proposing that chemical-specific considerations be considered to

determine whether the use of composite data from reduced-rate field trials are acceptable. Alternatively, a "decomposition" procedure may be judged appropriate. Please comment on whether these concerns are justified and, if so, how they should be addressed by OPP.

- In performing the regression analysis for bridging studies, OPP has elected not to "force" the regression relationship through zero, despite the fact that an application rate of 0 lbs ai/A would be expected to result in a zero ppm concentration in the plant or plant part. Please comment on this decision and any required changes in interpretation of the statistical parameters which a decision to force the regression through zero would entail.

- OPP intends to combine the bridging study and residue decline study guidance documents into one document. In so doing, would it be useful to expand the section on multiple regression techniques? How useful would this expansion be and are there any recommendations on how this could best be done?

- What other data or information similar to that described in this guidance document would provide a sound, empirical basis for determining residues at typical application rates for risk mitigation purposes?

To organize the comments received on these three papers, OPP has combined them into several larger topic areas:

- Science and Policy

- Risk Management Issues

- General Approach to Bridging and Residue Decline Data

- Processing/Cooking/Residue Degradation Data

- Residues in Meat and Milk

- Specific Guidance for Conducting Bridging and Residue Decline Studies

II. RESPONSE TO COMMENTS

A. Science and Policy

Overview. *Several commenters felt that the AR paper and others in the Tolerance Reassessment Advisory Committee (TRAC) series were actually risk management policies that are science based, rather than science policies. One commenter questioned the value of policy papers if the Agency could deviate from the policy at its discretion. A number of comments indicated a lack of clarity regarding the scope and applicability of the AR paper which had focused on OP pesticides.*

1. Separating Science and Policy

Comment. Several commenters felt that many of EPA's "science policies" are mislabeled. They are actually risk management policies that are science based. As such they should remain flexible enough to allow incorporation of evolving scientific knowledge.

Response. OPP acknowledges that there are both science and risk management policy matters discussed in the AR paper and in other science policy papers. For example, the number of field trials and residue samples, as well as the analytical and statistical methods for evaluating them may be considered science issues. Whereas, what constitutes a level of concern for food risk or what margin of safety is adequate are risk management decisions, albeit informed by scientific considerations. Further, OPP agrees that it is important to identify science issues and to separate them from risk management. For that reason, there is a separate section in this document for risk management issues raised by commenters. Regardless of whether these papers are regarded as risk management documents, science policy documents, or a mixture of both, OPP believes that the ideas they contain are worthy of a wide airing and public discussion.

2. The Practical Value of These Policy Papers

Comment. One commenter believed that the Agency's description of these policy papers would lead one to question their practical value. The *Federal Register* notice for each paper describes it as a policy document and not a binding rule; the commenter was concerned with the phrase in the document "on a case-by-case basis, EPA will decide whether it is appropriate to depart from the guidance...." He stated that the phrase "case-by-case" can cover a "multitude of sins," and that "one is left with the impression of documents written in sand." The commenter stated that the *Federal Register* notices commit the Agency to explain its departures from the policy documents and the Agency should hold to this commitment strictly, making clear the impact of each deviation on particular risk assessments.

Response. Any deviations will be explained in OPP's risk assessments and will be supported by a full and open risk characterization. An inherent feature of guidance is that it is not binding on either the Agency, the regulated industry, or members of the public. Decisions following the guidance cite it not as authority for the decision but as an explanation for the reasonableness of the decision. If OPP departs from the guidance, it will separately provide an explanation for its decision.

3. Scope and Applicability of the Anticipated Residue Paper

Comment. Many commenters noted that the approach described in the AR paper for using various types of data to refine residue estimates should extend to all of EPA's pesticide residue assessments, not just the OP assessments currently underway.

Response. In the draft AR paper, the Agency's intent was to seek information from the public on the nature and extent of existing data of the sort described in the paper for all pesticides. The draft paper noted a specific interest in these types of data for OP's because that large class of pesticides was (and still is) under evaluation by EPA. The Agency did not intend to limit the proposed policy only to OP's. The revised document includes this clarification.

Comment. One respondent suggested that before any data are developed, EPA and registrants should determine where these data would have a meaningful effect. If a given crop is not a significant contributor to risk or if residues at the limit of detection (LOD) or limit of quantification (LOQ) already present a risk concern, additional data would not likely address the risk adequately.

Response. OPP agrees that focusing on risk "drivers" is prudent. Because the drivers in a dietary risk assessment based on residues in food are not always obvious, OPP has incorporated into its assessment a CEC (Critical Exposure Contributors) analysis feature of the Dietary Exposure Evaluation Model (DEEM™) software that enables OPP to identify for registrants and all other interested stakeholders which commodities are the greatest contributors to the dietary risk from food for a specific chemical. Furthermore, as part of the public participation process developed by TRAC for the OP's, and soon to be extended to all chemicals in reregistration, the Agency generates a "Summary" and "Overview" of the risk assessment identifying risks of concern and the significant risk drivers if any. It should be noted that not all dietary assessments have drivers. In some instances, many commodities have essentially similar contributions to the overall risk.

4. Role of Monitoring Data in Refining Anticipated Residues

Comment. Several commenters noted that while they had no objection to the Agency's use of bridging, decline, and other data to refine residue estimates, it would be far preferable to expand the U.S. Department of Agriculture's (USDA) Pesticide Data Program (PDP) and other monitoring programs. Monitoring data, they pointed out, are the most realistic data available since they represent the amount of pesticide residue found on foods near the point of consumption.

Response. EPA acknowledges its preference for using PDP and other appropriate monitoring data in most instances for assessing dietary risk from residues in food, when such data are available. The Agency has developed methods to use PDP data to the greatest extent possible in its assessments (EPA 1999h). For example, PDP data are analyzed as composite samples, and EPA had previously used these data only for blended commodities. However, the Agency and other interested parties recently presented to the FIFRA Scientific Advisory Panel (SAP) several statistical methods to "decomposite" the samples. This allows for estimation of the range of possible residue values in single food items within a composite sample. Furthermore, OPP translates residue values from sampled commodities to similar commodities treated with the same pesticide. OPP, for example, would generally use the sampled residue value from oranges for grapefruit, and other citrus fruits, if no samples were available for those other fruits.

It must be noted, however, that due to the cost of monitoring and the limits on available funding, PDP and other monitoring data are not available for all food commodities, nor are they available for all pesticides. EPA works closely with USDA, the agency that administers the PDP program, to determine which pesticides, metabolites, and food commodities are most critical to monitor, and what modifications can be made to the program each year.

In summary, for conducting dietary assessments for residues in food, monitoring data are generally preferable to residue decline or bridging data. Cooking and processing data can be used in addition to monitoring data to further refine such estimates.

Finally, in discussing the applicability of residue decline and bridging studies, it should be noted the these types of data have utility beyond dietary risk assessments. For example, bridging data can be used to estimate an appropriate modified application rate, if a pesticide's application rate needs to be reduced due to risk concerns. Similarly, residue decline data could be used to establish an appropriate PHI. In both cases, it would be less costly to conduct decline and/or bridging studies than to recreate the entire residue data set for a given crop.

5. Other Sources of Monitoring Data

Comment. Several individuals suggested other sources of monitoring data including both public and private sources, and foreign field residue, processing, and monitoring data. For example, the high temperature hydrolysis study required by the European Union may be useful in providing residue degradation information as it mimics the effects of cooking.

Response. In some instances OPP has contacted commenters regarding the availability of monitoring data. In general, OPP has found that many processors monitor for pesticide residues, but few of these monitoring programs are able to link actual pesticide treatments in the field to residues in the finished commodity–information that is essential to determine the rate or percentage of residue decline. Furthermore, most companies and processors are willing to provide monitoring data only when a specific need is identified by OPP.

6. Refinements Should Not be Applied in Some Instances

Comment. EPA assessments need to take into account the fact that farm children are more likely to consume foods shortly after harvest, and thus with more residues, than nonfarm consumers. Residue degradation and decline studies would apply much less to these children than to the "average" population. Other situations not accounted for in EPA's draft policy are families who grow their own food, pick-your-own farm operations, and roadside stands. EPA needs to account for the child who "binges" on grapes or peaches at certain times of the year. EPA should not assume 100% cooking or peeling, not even for potatoes or meat (many eat meat very rare or as steak tartare).

Response. OPP does not assess potential exposures from food that might be obtained from roadside stands or "pick-your-own" operations *per se* due to lack of data on how many people consume foods from these sources and what proportion of their individual diets is from such sources. However, OPP anticipates that a very small percentage of the U.S. population derives more than a negligible portion of their food in this manner. Moreover, some harvested crops are distributed so quickly to wholesale and retail outlets that the residues in them would be very similar to the levels in crops sold near where they are grown.

OPP recognizes that binge eating can occur (and is not uncommon among children who may preferentially consume one food or class of foods). This phenomenon is captured by the food consumption survey database that OPP uses in its assessments (USDA's Continuing Survey of Food Intake by Individuals, which is commonly known as CSFII). In addition we note that the USDA Supplemental Children's Survey, which was developed by USDA at EPA's request, will soon be incorporated with the 1994-96 CSFII and will increase by five-fold the number of children ages one to five sampled. Furthermore, by looking at the 99.9% of exposure, OPP's assessments capture those individuals who consume large amounts of a given food item.

Finally, with regard to the assumptions that OPP uses related to cooking and peeling, the USDA consumption survey contains specific information about the form of the food that is consumed. If, for example, an individual in the survey reports eating an uncooked potato, or unpeeled kiwi fruit, OPP would not apply a cooking factor or peeling factor to the commodity consumed by that individual. In the 1989-91 and 1994-96 consumption surveys, for example, no individual reported eating uncooked meat.

B. Risk Management

Overview. *A variety of comments were related to risk management issues associated with the Agency's proposed policy to use various types of data to refine residue estimates. The draft policy did not specifically address risk management and stated only that if data were deemed to be adequate for risk assessment purposes, they would be considered in the on-going reviews of the OP's. The process for public involvement in reviewing the OP's was developed by the TRAC, and consists of six Phases, including two public comment periods–one focused on the preliminary risk assessment and another focused on development of appropriate risk mitigation. The time for submitting data to refine AR's ideally would be no later than during the 60-day public comment period on the individual active ingredient--Phase 3 of the TRAC process. The draft policy further noted that even if the dietary risk from an individual chemical was not of concern, registrants or others might wish to develop data to further refine residue estimates prior to the cumulative phase of the OP assessment. Several comments are beyond the scope of the current guidance. Nonetheless, they are summarized here with references to other, more appropriate policy papers and areas for discussion. Additional clarification is provided below.*

1. Modify Labels to Reflect Lower Rates

Comment. One commenter felt that if EPA used a range of "typical" application rates (and residues) in its assessments, then pesticide product labels should be amended to reflect those more restrictive parameters. There is no mechanism to enforce typical use rates and PHI's, and unless labels are modified, typical use patterns could shift toward higher residues over time.

Response. OPP desires to produce pesticide exposure estimates that approximate, as closely as possible, actual exposures that occur in the real world. It is also OPP's intention that its exposure and risk estimates not *underestimate* actual exposures, and OPP's risk assessment practices and policies are developed and implemented with this goal in mind. The commenter appears to believe that the use of a range of typical application rates in a probabilistic risk assessment necessitates that the labels be amended to reflect these more restrictive parameters and is concerned that there is no mechanism to enforce typical use rates and PHI's. OPP disagrees with the commenter. The purpose of a probabilistic risk assessment is not to restrict usage or enforce rates *per se*, but rather to develop

estimates of exposure and risk that reflect as accurately as possible *actual* use and usage practices, which include the range of typical application rates. OPP believes that appropriately considering the full range and probabilities associated with real-world pesticide application practices and, when available, incorporating this information into Agency risk assessments is consistent with the spirit, intent, and intrinsic principles of probabilistic risk assessment and with EPA's responsibility to assure that tolerances are safe.

OPP, however, does agree with the commenter that typical use patterns could shift toward increased use and increased residues. The Food Quality Protection Act of 1996 (FQPA) requires the Agency, in those instances where anticipated residue estimates are incorporated into an OPP assessment, to verify in five years, and thereafter as EPA deems appropriate, that the estimates incorporated by OPP in its risk assessment are still valid (see section 408(b)(2)(E)(ii)). Thus, the commenter is correct in that shifting typical use patterns could result in higher residues with time, but under FQPA the Agency is required to periodically re-evaluate these data and adjust its risk estimates, when necessary.

OPP also does agree that *under certain circumstances* label modification to reflect lower application rates and/or increased PHI's will be necessary. For example, if EPA's probabilistic assessment indicated that dietary exposures are above levels of concern, the Agency could require that labels be modified to reflect the lower application rates or longer PHI's that reflect more typical rates or PHI's. However, this resulting lowering of label rates is a result of risk mitigation/management activities, not a result of a need to "lock in" maximum label application rates used in the risk assessment.

2. How Data Will Be Used

Comment. Some commenters indicated that it was not clear how the types of data described in the draft policy would be used. One commenter noted that the policy suggests EPA cannot depart from the use of tolerance or field trial values unless it has chemical/crop specific data.

Response. EPA agrees that it is important to put the proposed residue refinements into the proper perspective. OPP has made several clarifications to the policy. First, as discussed above in response A-4, OPP uses PDP and other monitoring data to the greatest extent possible in both acute and chronic dietary (food) risk assessments. Residue decline, degradation, and bridging data would generally be of greatest value if PDP or other monitoring data were not available, or if the monitoring data do not represent recent changes to the use practices. Cooking or processing data however, could be used in addition to monitoring data to further refine residue estimates. For example, PDP may have residue data for a specific pesticide used on potatoes. These data already reflect the range of application rates and PHI's that were actually used. However, residue reduction factors derived from cooking data (*e.g.*, boiling, baking, microwaving, frying) could still be applied because these would reflect changes in residue levels *subsequent* to PDP sampling.

Which refinements are most appropriate for a specific crop and chemical may differ depending on the properties of the chemical and the types of crops treated with it. For example, is the crop eaten fresh, is it typically stored for a long period of time, is it typically washed, peeled, canned or frozen, *etc*.

3. A Short-Term Management Strategy is Needed

Comment. Several commenters felt that the draft policy did not address the short-term problem, *i.e.*, the need for appropriate data to refine residue estimates for the OP pesticides that are currently under review. One commenter suggested that FFDCA section 408(b)(2)(E) allows EPA to estimate anticipated residue levels even if no actual crop-specific data are available so long as EPA calls in confirmatory data within five years.

Response. EPA, in conjunction with the TRAC, has established a process for public review and participation of the tolerance reassessment of the OP's. Within this process EPA makes preliminary risk assessments available and holds stakeholder meetings and technical briefings to explain the assessments and discuss data gaps. It is during this process that EPA meets with registrants, growers, and other interested parties to determine what refinements can or should be made to risk assessments and to develop interim risk mitigation strategies. EPA does not believe that a separate short-term management strategy is needed because the TRAC process has proven to be an effective way of working through risk refinements and mitigation, including identifying and developing data that may be necessary to confirm that residues are actually lower than preliminary estimates suggest.

EPA agrees, in part, with the commenter's construction of section 408(b)(2)(E). That provision states that EPA "may consider available data and information on the anticipated residue levels of the pesticide chemical in or on food and the actual residue levels of the pesticide chemical that have been measured in food, including residue data collected by the Food and Drug Administration." If EPA relies on such data or information, it must call-in data to be provided five years after the tolerance action, "and thereafter as [EPA] deems appropriate, demonstrating that such residue levels are not above the levels so relied on." EPA would agree that this provision does not limit EPA to estimating anticipated residue levels only where actual crop-specific data on the food in question are available. By referring to "available data" the Agency is given discretion to consider any data that bear on residue levels, including data from the same pesticide on other crops or similar pesticides. Such data could be used to extrapolate

or model anticipated residue levels in the food in question in appropriate circumstances. EPA's use of such extrapolations or models is tempered, as always, by section 408(b)(2)(D)'s command that EPA consider the reliability of the available data. EPA does not agree with the commenter's interpretation of section 408(b)(2)(E) to the extent that the commenter is suggesting that Congress intended that the initial estimate of anticipated residues need be no more than a mere "prediction" of residue levels with the subsequent data being used to confirm that prediction. Rather, EPA's view is that the initial estimate of anticipated residues must be reasonable based on the available data. Subsequent data call-ins would then be used to verify that, over time, conditions had not changed such that the anticipated residue levels had risen to such a level that a risk of concern was created. For example, the statute specifically authorizes use of Food and Drug Administration (FDA) monitoring data in making an estimate of anticipated residues. Where that is the case, EPA would probably require submission of similar monitoring data be provided five years later to verify that use patterns had not significantly altered residue levels.

4. Do Not Delay Risk Management Pending Data Development

Comment. Several commenters urged EPA not to wait for data (including the types of residue refinement data described in the draft policy), if there are other risks of concern; for example, high risk to workers handling and applying the pesticide. Delaying action in the name of "refinements" is side-stepping the Agency's responsibility to protect children's health and workers. The commenter cited a report by the Environmental Working Group (EWG) that used government residue data and showed some residues on single serving sizes alone exceed EPA’s level of concern. Another commenter noted that to avoid wasting resources EPA should evaluate the utility of additional studies in the context of the overall risk of the chemical. Pesticides with unacceptable risks using method limits have outstripped our ability to measure and EPA should discourage use of these.

Response. Generally, EPA conducts a full exposure and risk assessment based on the best available data. For the OP's, the TRAC process provides for public review, refinement of EPA's assessments and development of risk mitigation on an orderly, equitable schedule. During this process EPA does evaluate the overall risk of the chemical and would not delay worker or ecological mitigation pending development of data to refine the dietary assessment. A process similar to the TRAC process for OP's has been proposed for all chemicals in reregistration (see 65 FR 14199; March 15, 2000). Registrants may choose to conduct additional bridging or residue decline studies and submit them in a timely manner for EPA to use in refining its dietary exposure estimates, but EPA will not delay the process.

5. Presumptive Use of the 10-Fold Safety Factor

Comment. One commenter felt that EPA should make "presumptive" use of the 10-fold safety factor based on: failure of current required toxicity tests to assess all toxic effects of concern for fetus, infant, and child; untested potential for endocrine disruption; failure of current testing regime to monitor effects to test animal for a full lifetime; EPA's use of constantly more refined estimates that remove previous, more protective assumptions that provided some margin of safety; lack of comprehensive and reliable data on children's nondietary exposure; and lack of good monitoring data for drinking water.

Response. EPA's position on the use of the 10-fold safety factor is beyond the scope of this policy paper. For information on that topic, the reader is referred to the draft policy papers entitled, "Standard Operating Procedures for the Health Effects Division FQPA Safety Factor Committee" (EPA 1999d) and "The Office of Pesticide Programs' Policy on Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process" (EPA 1999e). Both are available on the internet; the addresses are listed in the References. This comment will be considered as EPA reviews other comments submitted on these two papers and decides whether and how to revise them.

C. General Approach to Bridging and Residue Decline Data

Overview. *In the AR paper, EPA was seeking information from the public on the nature and extent of existing data that could be used to refine residue estimates. The Agency had hoped to gather comments drawing on the combined experience of those who had conducted these types of studies previously and apply them to the development of Agency guidance for conducting bridging and residue decline studies. While many commenters supported the general approach outlined in the paper, only one company made reference to market basket data under development, and no actual data were provided during the comment period. Several comments were received on specific aspects of the general approach and the policy has been revised to reflect most of these.*

1. Existing Data

Comment. A general theme throughout the comments was that the types of data described in the AR paper were not commonly available. One commenter noted that companies rarely generate multiple application rate data due to cost, and that residue decline data are part of the current residue chemistry guidelines, but are not generally available for older pesticides. Another noted that few such studies exist because up to now there had been no need to perform them.

Response. EPA appreciates this information. Absent these data, OPP will rely on its standard practices and procedures. The policy does not require new or additional data, rather it permits these data to be used if they are available.

2. Relationship Between Application Rate/PHI and the Resulting Residues

Comment. Several commenters addressed the nature of the relationship between reduced application rates and resulting residues, and increased PHI's and resulting residues. One noted a clear linear trend between residue level and application rate under certain circumstances when looking at average residue values for each application rate. The same commenter agreed with EPA's assertion that there is not a general relationship between different PHI's and residue levels. Other commenters noted that the relationship between different application rates and residues was not linear, and the relationship between different PHI's and residues is chemistry dependent. No actual data were provided to support these hypotheses.

Response. EPA's purpose in posing the question about the relationship between application rates/PHI's and residues was to determine whether or not existing bridging or residue decline data could legitimately be translated among chemicals and/or crops. In the absence of a body of data to demonstrate the nature and predictability of these relationships, such generalizations cannot be made.

3. Number and Location of Field Trial and Samples

Comment. Many commenters agreed that three replicates per site and one to three sites per study were appropriate. No alternative sampling regimes were suggested. One commenter did note that three replicates was a departure from the current requirement of two replicates for residue work. The same commenter urged EPA to reconsider the specification to have the three field trials in the area of highest production, the area of highest average field trial (HAFT) value, and the area of the second HAFT. The rationale for this request was so that bridging and/or decline data could be done concurrently with magnitude of the residue programs, *i.e.,* the initial battery of residue tests that are conducted to support registration of a chemical for a food use. The commenter further suggested that, in the absence of existing magnitude of the residue data, the diversity of geographic conditions could be captured, for example, by conducting one trial in California, one in the South, and one in the mid-West. Another

commenter echoed the sentiment by suggesting that EPA could incorporate additional treatment regimes more representative of typical use rates into the preexisting guidelines (OPPTS 860.1520; EPA 1996a).

Response. EPA acknowledges that three replicates is a departure from current guidance, but believes the additional replicate is justified by better accounting for true variability. The Agency also agrees that modifying the guidance to allow for concurrent development of magnitude of the residue and bridging data is appropriate and has done so.

Comment. A related comment requested clarification on whether the Agency intended to use single data points (replicates) or averages of the data points.

Response. OPP has clarified the guidance to reflect its intention to use single data points rather than averages.

4. Role of Usage Data

Comment. Several commenters requested that OPP clarify what was meant by "reliable usage data." The draft policy indicated that bridging and decline data could only be used in probabilistic dietary assessments if coupled with reliable usage data indicating what percentage of the crop is treated at various application rates and what percentage of a crop is harvested at various intervals after the last pesticide application. Other commenters felt that the lack of usage data should not be an impediment. The IWG and others suggested that the FFDCA section 408(b)(2)(E) supports using "available data and information" and requiring actual data within five years to verify that the anticipated residue has not increased.

Response. The most complete description of "reliable usage data" can be found in a companion science policy paper entitled, "The Role of the Use-Related Information in Pesticide Risk Assessment and Risk Management" (EPA 1999f). It was issued for comment in July 1999, and a revised document is expected shortly. To summarize briefly, EPA primarily relies on USDA sources and land grant universities as well as proprietary sources, such as Doane's for use and usage. These sources taken together are generally adequate to determine the range of typical application rates for major crops. Information on the range of typical PHI's is not readily available. For minor crops and unusual situations, EPA usually contacts field extension offices, crop advisors, registrants, or growers. In actual practice, EPA makes every effort to obtain and verify appropriate usage data for its assessments. Recent examples include the Technical Briefings that OPP has held for most OP pesticides, where OPP has identified areas where usage data would be helpful in refining risk estimates and growers have provided it. Also of note are the "Crop Profiles" developed by EPA and USDA. As indicated above in B.3., EPA does not agree with the IWG comment to the extent it suggests that available data on anticipated residues need not be reliable.

5. Use of Percent Crop Treated for Acute Dietary Assessments

Comment. One commenter felt that OPP should not use percent crop treated (PCT) calculations in acute dietary risk assessments. They reasoned that any amount of a crop treated at a level that will render acute harm (*e.g.*, the hot potato) to someone cannot be characterized as assuring "reasonable certainty of no harm." According to the commenter's interpretation, section 408(b)(2)(F) of FFDCA specifically authorizes EPA to consider PCT "when assessing chronic dietary risk..." and then only if the Administrator makes specific findings about data reliability. This express statement gives rise to their conclusion that Congress did not intend for EPA to use PCT in estimating acute dietary risk.

Response. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and FQPA are silent on the issue of whether EPA can use PCT adjustments for acute dietary (food) risk assessments. In fact, the statutory language is constructed to place certain restrictions on the use of PCT information in chronic risk assessments which suggests that Congress was merely setting out rules for the use of PCT information in these situations, not making a broader statement about use of this information generally. Furthermore, and perhaps more importantly, the use of PCT information in probabilistic acute assessments not only allows the Agency to take into account the "hot potato," but also the probability that a high level of exposure will occur. In other words, if some percentage of a crop is not treated this would lower the probability that a consumer would eat a treated commodity, but not alter the range of estimates of the residue levels on that treated commodity.

6. Extrapolation to Similar Crops

Comment. Several commenters supported the idea of extrapolating residue decline and bridging data to similar crops. One suggested that EPA needs to develop and issue a list of surrogate crops. Another suggested using crop groupings or "indicator" crops to allow for translating data. He further observed that it should be possible to examine residue data regarding crops for which there are both field trial and PDP data, determine the ratio of the respective ranges of the values, and develop reasonable rules for short-term use to convert field trial values downward for crops where PDP data are lacking. Another comment expanded this idea to include translating data among similar pesticides on a particular crop.

Response. EPA believes that it is reasonable to use the same crop groupings for bridging and decline studies as those used for other residue data development (see 40 CFR §180.41). For example, if bridging data were developed for a specific chemical on a representative pome fruit commodity, *e.g.*, apples or pears, the resulting factors could also be applied to all members of the pome fruit group. As additional data become available, these translation groups may be expanded. However, EPA currently has no reason to believe that developing generic ratios between field trial values and PDP monitoring values for application to crops that

are not monitored by PDP would be scientifically valid, or adequately protective of public health. We note that there can be tremendous pesticide chemical-to-pesticide chemical variability with respect to degradation/metabolism, system vs. non-systemic nature of the pesticide chemical, application method, etc. Developing such “rough rules of thumb” would be problematic for crop-to-crop translations as well since timing and rate of application, crop morphology, harvest times, etc. could vary significantly. Nevertheless, if a registrant is able to generate adequate justification and scientific support for such extrapolations, this information could be considered on a case-by-case basis.

See also response F5, below

7. Residue Data Should Reflect All Metabolites of Concern

Comment. One commenter voiced the concern that if the Agency does allow submission of additional residue data, those data should reflect all residues of toxicological concern. In addition, where field trials are conducted at PHI’s, or preslaughter intervals for livestock, longer than current label intervals, additional metabolites may be produced during the longer intervals. The Agency should require metabolism studies consistent with the longer intervals, if such data are not already available. The commenter's concern was based on his belief that the conventional chemical model for OP cholinesterase inhibition is a P=O (or P=S) bond, and three bonds of P-OR and/or P-SR, where R represents side chains such as aryl or alkyl groups. Metabolism that modifies side chains without cleaving O-R or S-R bonds will retain, or even increase, cholinesterase inhibition.

Response. EPA acknowledges that the scenario suggested is theoretically possible but not likely. The preponderance of evidence in the open literature suggests that OP’s break down readily and that the P=O bond is the first to break, rendering the resulting moieties incapable of inhibiting cholinesterase. EPA's current data development process provides for the identification of metabolites of concern based on nature of the residue studies. Magnitude of the residue studies in plants and/or livestock are then required to measure the magnitude or amount of each metabolite of concern. If there were reason to suspect that new or higher levels of previously identified metabolites of concern would be

produced under conditions of longer PHI's, EPA would require these data. In the case of the OP's, this does not appear to be warranted.

D. Processing/Cooking/Residue Degradation Data

Overview. *The draft AR paper also described processing, cooking, market basket and residue degradation (storage) data, although in less detail than the bridging and decline data, and how these data could also be used to refine anticipated residue estimates. Relatively few comments addressed these studies. One commenter provided references to numerous degradation and processing studies that his company had conducted.*

1. Food Processing Practices

Comment. One commenter noted that in brief discussions with the food processing industry, he found that processing procedures vary by region and processor. Included with the comments was a listing of processing studies performed with methomyl that the commenter felt were excellent examples of food industry and household preparation processing studies, and recommended that the Agency develop future guidelines for these types of studies based on these study designs for methomyl. Finally, he noted that dramatic reductions of residue levels were seen after following typical food industry and household preparation practices. Some of the topics addressed in the methomyl studies are: the magnitude of residues in head lettuce after normal trimming and washing, magnitude of residues in apple fruit after packing plant processing and cooking, magnitude of residue in fresh and canned succulent green beans, and magnitude of the residue in orange fruit processed through a packing line.

Response. EPA agrees that significant reduction in residue levels are commonly seen following typical food industry and household preparation practices. For this reason the Agency encourages submission of studies that allow us to quantify these reductions. EPA also agrees that processing practices vary from region-to-region and from processor-to-processor. For this reason, several processing studies may be needed to adequately characterize the variability in processing practices. EPA also agrees that the referenced methomyl studies are acceptable examples of processing studies and has used this information in its dietary assessment of methomyl for reregistration.

2. Consider Metabolites Produced from Heating/Cooking

Comment. One commenter cautioned that if the Agency allows cooking studies, it should recognize that metabolites produced by heat may be different from those produced during use on crops and livestock. The Agency should require that heating and cooking studies be conducted similarly to metabolism studies, so additional residues of toxicological concern may be identified. Because OP's comprise a range of chemical structures and side chains, extrapolation of heating and cooking data from one OP to another should generally not be done.

Response. Based on existing literature for the OP's, these compounds appear to break down rapidly on heating. OPP would not require additional metabolism data for cooking studies with OP's.

3. No Guidance for Degradation Studies

Comment. One commenter noted that OPP currently does not have guidance for conducting degradation studies.

Response. OPP does not have separate guidance for residue degradation studies, *i.e.*, studies that measure residue decline in commodities that are typically stored for long periods of time. However, methods for conducting degradation studies would parallel those for residue decline studies.

E. Residues in Meat and Milk

Overview. *In the draft AR paper, EPA described a number of studies that could be used to refine estimates of pesticide residues, particularly OP's, in meat and milk. Only two commenters addressed this topic.*

1. Use a More Realistic Animal Diet

Comment. One commenter suggested that such refinements as indicated in the AR paper were appropriate, but felt that it would be more productive for EPA to use more realistic assumptions related to actual animal diets.

Response. OPP's assessments currently assume that a relatively large portion of an animal's diet could be composed of items treated with the pesticide being assessed. However, OPP would *not* generally assume for a pesticide used on apples and cotton that livestock would consume *both* apple pomace or cotton gin trash since these items are present in livestock diets only in some regions of the country and during certain times of the year and would not generally be expected to be simultaneously present in any given animal's diet. This assumption is based on the fact that it is not economically feasible to transport these regional by-products out of the area where the commodities are produced. OPP is willing to modify its high-end animal diets if data are made available from growers, processors or other sources.

We note, too, that cooking data for meat and processing (pasteurization) data for milk would yield the most useful refinements since they would permit factors to be used to adjust residues in meat and milk that reflect residues on an "as consumed" basis.

2. No Finite Residues of Organophosphates

Comment. One commenter felt that all OP tolerances for meat and milk should be revoked under 40 CFR §180.6(a) since there is already ample evidence that OP residues are not found in these commodities. The same commenter provided references, but no actual data, to support his assertion that meat and milk tolerances are not needed for OP's. These included reference to: PDP monitoring data for milk for 1996-1997 showing only one detection of an OP (dichlorvos at 0.003 ppm) in approximately 60,000 samples; USDA's Food Safety Inspection Service (FSIS) previous testing of meat; and FARAD (Food Analysis Residue Avoidance Databank) data.

Response. EPA agrees that existing PDP and other monitoring data, as well as information in the literature, suggest that OP residues are not generally found in appreciable quantities in processed (pasteurized) milk. Nevertheless, the criteria for determining whether a tolerance is necessary is not based on whether actual detections in monitoring data or market basket surveys are common, but rather whether there is "no reasonable expectation of finite residues" in meat, milk, poultry and eggs following exaggerated rate feeding studies as prescribed under 40 CFR 180.6. It would serve little purpose, for example, to revoke a tolerance simply because a pesticide chemical is *rarely* used if, for example, residues *did* appear when it *was* used.

However, it is important for the commenter to remember that if monitoring data are available that show no (or very few) detections of a pesticide chemical, then it is these monitoring data, and not the tolerance, that is used in the risk assessment. For the example cited by the commenter in which ample PDP data on milk were available showing no (or very few) detections, the risk assessment would rely not on the tolerance (representing the maximum legal limit), but rather on the actual residues found in the monitoring program.

Finally, OPP would like to clarify the commenters remark on the number samples of milk collected by of PDP during 1996-7. The 60,000 *samples* referred to by the commenter is actually 60,000 database *records* where a database record is generated for each sample-analyte combination. Thus, if one sample were collected and analyzed for 30 analytes, a total of 30 *records* would be generated. Since PDP analyzes its samples for many pesticides, there are a significantly greater number of PDP database records than there are samples. During 1996, 1997, and 1998, PDP actually collected and analyzed 575, 732, and 595 milk samples, respectively.

F. Specific Guidance for Conducting Bridging and Reside Decline Studies

Overview. *A number of commenters responded specifically to the questions posed in EPA's draft guidance documents. Their comments and responses are detailed below.*

1. Clarity and Completeness of Guidance

Comment. One commenter indicated that the guidance provided in the document is clear and complete. However, the commenter indicated that he had some concern that the proposed procedures for dealing with the residue data were overly prescriptive and too dependent upon hypothesis testing and that this might lead to useful data being rejected for use in dietary risk assessment. The commenter suggested that simpler and more pragmatic interpretations of the data might be more appropriate and would lead to more efficient use of all available data. Another commenter stated that the guidance document provides explicit instructions on the analysis and interpretation of the potential results from these studies, but believed that a strict prescription on analytical methods can be problematic. The statistical procedures for dealing with the residue data from these trials, the commenter believed, are overly complex and prescriptive, and too dependent on hypothesis testing. The commenter continued, stating that useful data may be rejected for use in dietary risk assessment and that simpler and more pragmatic interpretations of the data might be more appropriate and lead to less waste of useful and expensive data.

Response. OPP appreciates the comments provided, and recognizes that the guidance may be seen as overly prescriptive in that it describes specific methods for estimating a relationship between application rate and residue level or PHI and residue level. However, registrants or other data submitters are not bound or committed to following this guidance in estimating that relationship; the guidance is only one means of estimating this relationship which OPP will find sufficiently statistically rigorous for use in quantitative risk assessment. It is not a strict prescriptive procedure. Acceptance or rejection of studies by OPP reviewers is not based on unwaivering adherence to guideline recommendations, but rather on the judgement of the reviewer of the specific study's scientific rigor and validity. OPP does not and will not automatically reject useful data for use in dietary risk assessment based solely on whether or not guideline recommendations are adhered to. The guidance presented here is only one method that attempts to take into account many of the concerns OPP may have about extrapolating simple ratios determined at one site at one application rate to many diverse sites at many potentially very different application rates.

2. Adequacy of the Residue Studies for Generating Refined Acute Dietary Probabilistic Exposure and Risk Assessments

Comment. One commenter indicated that the approach recommended by OPP is sensible; it is analogous to processing studies in which the objective is to establish the relationship between residues in the raw agricultural commodity (RAC) and those in the processed commodity and NOT to determine the magnitude of residues in the processed commodity. However, the commenter recommended that a limited number of studies be conducted in greenhouses. This approach would demonstrate the relationship between application rate and residue levels, but would not be influenced by weather conditions and other "weathering" influences.

Another commenter indicated that the studies would be helpful for refining the estimated exposure that would be suggested by use of worst-case field trial data at maximum application rates and minimum PHI. However, the commenter stated that monitoring information ordinarily will be even more useful in refining exposure and risk assessments.

Response. With respect to the comment concerning the conduct of these studies in greenhouses, OPP believes that this could not be used for residue decline studies, but could be considered for bridging studies. OPP would recommend that any interested party contact OPP for additional information regarding such greenhouse trials prior to study initiation.

OPP agrees with the commenter that monitoring information is more useful than field trial data in refining exposure and risk assessments. As a rule, monitoring data will have precedence over "adjusted" field trial values in the risk assessment process. Only when adequate monitoring data are not available will values from experimental crop field trials (adjusted or not) potentially be used in a risk assessment.

3. Adequacy of Recommended Studies to Establish a Rate *vs*. Residue or PHI *vs*. Residue Relationship

Comment. Several commenters indicated that these recommendations are reasonable and should provide useful data to generate probabilistic exposure and risk information.

Another commenter indicated that the residue studies appear to strike a reasonable balance between the expense of conducting a full suite of studies to attempt to determine the relationship of interest *vs.* a smaller set of bridging study or residue decline studies. Specifically, the scheme to link the number of bridging studies to the number of field trials required for setting tolerances is reasonable and the number of trials appears to be in keeping with the numbers of trials required. However, the commenter questioned whether the requirement for three composite samples will increase the amount of information enough to justify increasing study analytical costs by at least one-third. Requesting triplicate composite samples at each time point implies that the variability at each time point is the key sensitivity in the

overall dietary assessment. The commenter believed that this theory was untested and that additional effort and expense might be better spent on getting better precision on the use rate distribution assumptions or market share. The commenter noted that the residue chemistry guidelines recommend two samples, although one sample is acceptable.

Another commenter stated that in the experience of at least one registrant, data of the sort discussed in the policy paper tend to show a linear relationship between initial application rate and residues at a given PHI. In many cases, the line is very good and parallel lines will be obtained for different PHI's from studies done at the same time and site. However, studies at different sites may vary considerably due to the differences in growing conditions. The examples given by EPA demonstrate analyzing the data for all sites in combination, and provide some alternatives in the cases where different sites give different results. The commenter was unsure whether finding similar results in widely varied geographical areas will be the exception and not the rule. The commenter also reminded the Agency that decline studies would need to be free of any unusual rainfall events or other weather-related conditions that could skew the residue data. Thus, the studies submitted would all have to yield acceptable data.

Response. OPP believes that three composite samples strike a reasonable balance between the analytical cost of a third sample and the additional information regarding within-field variability. The use of three samples also helps to confirm the absence of heterskedasticity which is an important prerequisite for Ordinary Least Squares Regression and the resulting statistical inferences regarding significance. In addition, current Occupational and Residential guidelines recommend triplicate analysis of all samples.

4. Appropriateness of Deriving a Quantitative Relationship Between Application Rate and Residue Level on Residues That Are Below the Limit of Quantification

Comment. One commenter disagreed with the recommendation against the use of rates that would lead to nonquantifiable residues and believes that this decision should be made on a case-by-case basis by the registrant. The commenter agreed that a quantified value will be needed to represent the residue from a maximum rate/minimum PHI application, but stated that this should not be required for seed treatment studies or lower rate/longer PHI residue testing. The LOQ, the commenter stated, could be used as a conservative surrogate and any resulting uncertainty would result from overestimation of exposure, not underestimation. The commenter agreed that the registrant or other study contractor should be free to seek a fully quantified ratio by use of exaggerated rates, but that it should not be required.

Another commenter agreed with the previous commenter that having quantified values for all points to be used in the comparisons is highly desirable, that quantified residues will be needed to represent the residues resulting from maximum rate/minimum PHI, and that useful information could be derived by using an LOQ as a conservative surrogate for the ND values. The commenter stated that it would be hard to derive a quantitative relationship between rate and/or PHI on the one hand and residue level on the other if some residues fall below the LOD (but not the LOQ). However, the commenter indicated that there is still value if the residue levels are between the LOD and LOQ and that it is acceptable to estimate a residue level between LOQ and LOD for use in developing the quantitative relationship, given the large inherent variation normally associated with residue testing, even at residue levels above the LOQ. The commenter acknowledged, however, that it would not be appropriate to use ½ LOQ residue values in determining residue decline curves.

Another commenter believed that the suggestion to use exaggerated application rates to achieve quantitative measurements is reasonable. However, the commenter believed that the constraint regarding the adjustment of nonquantitative residues should be reconsidered for at least one case. If values are below the LOD, the commenter believed it appropriate to divide the study LOQ by the exaggeration factor.

Response. The purpose of the policy guidance document recommendation that measurements below the LOQ not be used in quantitative regression analysis in determining the effect application rate (or PHI) has on residue levels is to encourage the use of exaggerated rates such that residue measurements can be adequately quantified. The OPP reviewer, in all cases, can use his or her judgement and conclude that incorporation of below quantification level (BQL) or below detection level (BDL) measurements into quantitative estimates of this relationship is appropriate, depending on the specifics of the case. In these situations, OPP will likely investigate the robustness of the regression analysis by performing a sensitivity analysis of the regression relationship. That is, the sensitivity of the final estimated relationship to assumptions regarding the value associated with the BQL or BDL can be assessed to determine if incorporation of BQL or BDL measurement might significantly affect the outcome of the study or assessment.[1]

Nevertheless, OPP believes that the concern about a potential preponderance of BQL or BDL values when field trials are conducted at 1x and lower rates is misplaced. BDL and BQL values generally do not affect OPP dietary risk estimates and it is doubtful that bridging or residue decline studies would be conducted on crops for which BQL or BDL residues are expected.

[1]In any case, if it is determined that it is appropriate to incorporate BQL limits into a quantitative regression relationship, then it is important that the actual estimated value (and not a default value of ½ LOQ) be incorporated

5. Extrapolation of Data between Similar Crops

Comment. One commenter believed that expanded extrapolations should be considered. For example, if a pesticide's use directions are the same for several crop groups (*e.g.*, leafy vegetables, fruiting vegetables, cucurbit vegetables, and *Brassica* vegetables) or similar crop subgroups (*e.g.*, leafy greens and leafy *Brassica* greens) and have resulted in the same established tolerances for each of the crop groups, then data should be able to be translated between those groups/subgroups.

Another commenter believed that the Health Effects Division's Standard Operating Procedure (SOP) 99.3 on permissible crop translations (EPA 1999g) would provide a good rationale for the extrapolation of data. It is based on the crop groupings, is quite clear, and should be suitable as a starting point. The commenter stated that more extensive extrapolation across crop groups from the data may be appropriate as well. The commenter suggested, for example, that extrapolation should be allowed among leafy vegetables, *Brassica* vegetables, leave of root and tuber vegetables, and foliage of legume crops; and among root and tuber vegetables and bulb vegetables. Additional translation across other crop groups should be more fully explored. The commenter also indicated the hope that OPP will make an effort to include in any data translation scheme those crops that are not assigned to crop groups (*e.g.*, grapes, peanuts, strawberries, *etc*.). The commenter believed that similar rates of decline will generally be seen regardless of the crop. In addition, the commenter believed that if a linear relationship is observed across suitable representative crops (*e.g.*, fruit, leafy vegetables, and cereal crop), then the Agency should conclude for this product that a linear relationship exists between the application rate and residue level for all crops.

Another commenter believed that extrapolation between crops outside the same crop group can be made as long as the general crop morphologies, cultural practices, and use patterns are similar. For example, if use patterns are similar, it may be reasonable to extrapolate between pome fruits and stone fruits, but not between pome fruits and caneberries. The commenter believed that such an extrapolation is reasonable because the point of the exercise is not to extrapolate residue values between the crops, rather to extrapolate relationships between different PHI's (and application rates).

Another commenter indicated that the guidance provided in the document was clear, but additional examples should be provided for crop surrogation. In particular, the commenter indicated that an example data set for which extrapolation would be accepted would be quite instructive and that such examples could include the rationale for why extrapolation would or would not be deemed appropriate.

Response. The document has been revised to make clear the recommended crop-to-crop extrapolations. Specifically, the crop group or subgroup extrapolations described in 40 CFR are recommended. At this time, any further extrapolations will be made only on a case-by-case basis as determined by the OPP reviewer. In the future, crop-to-crop extrapolations may be expanded, perhaps considerably, as additional studies are submitted for review and OPP gains experience across additional crops and trials. With very little data in hand, OPP is reluctant to expand these extrapolation procedures considerably beyond those currently used for crop field trial guidelines.

With respect to the commenter's request for additional examples on crop surrogation, the document has been revised such that a crop surrogation scheme has been more fully described. Specifically, the crop surrogation scheme that will be used to extend results from maximum application scenarios for field trials used to determine the tolerance to "real-world" typical application rates will be the same as that used to determine tolerances. That is, the crop surrogation scheme appearing in 40 CFR 180.41 will also apply to bridging and residue decline studies. On a case-by-case basis, it may be further extended.

6. Necessity of Having Reliable Usage Data Concerning

Application Rates and/or Preharvest Intervals

Comment. One commenter stated that the availability of "reliable use data" is still evolving. Many organizations, the commenter stated, are working on developing better use data for crop protection products. EPA, USDA, grower groups, and industry need to work cooperatively to develop better data on frequency of use of specific application rates and PHI's for a product.

Response. OPP agrees with the commenter and is working with industry, USDA, and grower groups to develop this information.

7. "Lack of Fit" Test

Comment. One commenter indicated the coefficient of determination is a measure of the "strength" of the linear relationship between the dependent and independent variables, as calculated by the proportionate reduction in the variance of the dependent variable that is due to conditioning on the independent variable. It is not a "test of fit" *per se*. The "lack of fit" test, on the other hand is used to test whether more complex models provide a better fit than the model under consideration.

Response. OPP agrees with the commenter. If a graphical representation of the data indicates significant departure from the linearity assumption, use of the LOF test may be recommended. Nevertheless, OPP will take into account all available information (coefficient of determination, graphical and residual analyses, and LOF tests) in determining whether an adequate regression equation has been developed.

8. The Effect of Compositing on Unit-to-Unit Variation

Comment. One commenter stated that he appreciated OPP's concern about eroding the inherent safety margin by basing probabilistic assessments on worst-case conditions. The concern arises, the commenter explained, because although compositing reduces the potential variability, this reduction in variability was "countered" by the fact that residues were generated under the worst-case label conditions. The commenter explained that the issue of concern is if one uses field trial data conducted at longer PHI's or lower application rates, then the amount of conservatism that was due to worst case label conditions is lost.

Another commenter indicated his belief that large sample-to-sample variation in residue levels is not common for single-serving commodities. The commenter continued, stating that studies by USDA on single-serving *vs*. composite residue variability should provide some insight on the significance of the concern on this issue. The commenter stated that while some decompositing methods are viable, they still overestimate the range of residues on the individual samples within the composite sample.

The commenter expressed concern about the policy document statement that guidance for a composite *vs*. single-serving variability study can be provided if a registrant believes that significant issues associated with variability may occur. The commenter indicated that this guidance should be provided as part of the policy since registrants need to understand all of the options before starting bridging and residue decline work.

Response. OPP is currently investigating the issue of decomposition and presented this to the SAP in March 2000 (EPA, 2000a). A final SAP report on this issue is expected inJune. OPP will carefully consider the recommendations of the SAP and the results of its investigation in determining if there might be significant concern about bridging and residue decline studies eroding the safety margins implied by the maximum rate/minimum PHI studies.

9. Not "Forcing" the Regression Relationship through Zero

Comment. One commenter stated that the “forcing” the regression through zero may give a spurious appearance to the regression line and results of such regression models cannot be compared to results of regression models that include an intercept. If the estimate of the intercept is not found to be significantly different from zero, this may be used as an indication that the regression can be forced through zero. However, with the type of data considered for bridging studies, the intercept is expected to be small if the linear model provides a good representation of the data, and including it in the regression model does not impact the results.

Response. OPP agrees with the commenter. The regression relationship is (in the vast majority of cases) expected to go through zero for bridging study results, but should not be “forced” through. In any case, minimal effect should be seen, particularly if recommendations are followed such that the minimum and maximum label rates are both used in establishing the regression relationship and extrapolation beyond this range is not required.

10. Multiple Regression Techniques

Comment. One commenter recommended expanding the discussion on multiple regression techniques, especially the discussion of assumptions underlying these methods. For instance, the commenter indicated that the users of the approach need to be aware of the independence, normality, and equal variance assumptions that are needed in linear regression models. The document suggests testing the equal variance assumption through the use of Bartlett or Levine’s tests, but notes that Bartlett’s test is sensitive to departures from normality while Levine’s test is not. The document does not mention the need to test for normality or the need to transform data.

One commenter indicated that many factors affect crop residues, and these papers only address two of these factors (application rate and PHI). The Agency suggests using multiple linear regression of these two factors to develop a mathematical model to predict crop residues. This is a potentially useful approach that could be extended. Other factors such as the number of applications, application interval, weather variables, and crop growth also affect crop residues. If the effects of these factors were really understood, then a more general mathematical approach could be developed. This would have benefits in enabling dietary risk assessments to be further refined, thereby narrowing the gap between regulatory exposure assessment and exposure of consumers in the real world.

Response. At this time, OPP does not intend to expand the discussion on multiple regression techniques. Registrants and other data submitters, however, are encouraged to perform simultaneous rate/residue decline studies if these are perceived to be economical ways of generating data.

With respect to the comment on the assumptions underlying the methods presented in the document, the document has been revised to explicitly describe the need for testing normality, transforming data, or investigating the characteristics of residuals.

11. Other Data or Information for Determining Residues at Typical Application Rates for Risk Mitigation Purposes

Comment. One commenter suggested that if residue studies show a linear relationship between application rate and residue levels over a range of crops, that data should be sufficient to allow development of a linear extrapolation model for residues at lower application rates.

Response. This issue has been detailed in a previous response.

12. Crop Enforcement Method

Comment. One commenter stated that it was not apparent in the two policy papers if the crop enforcement method must be used for this work and asked if it would be permissible to use a more sensitive method instead of the enforcement method. If the enforcement method was not used, would some additional bridging work be required to show equivalency of the methods?

Response. OPP has modified to document to clarify this issue. The use of an analytical method that is more sensitive than the enforcement method is permitted and even encouraged. No additional bridging work would be required to show the equivalency of the two methods.

III REFERENCES

EPA 1996a. "Residue Chemistry Test Guidelines OPPTS 860;" August 1996. http://www.epa.gov/docs/OPPTS_Harmonized/860_Residue_Chemistry_Test_Guidelines/Series/ (EPA 712-C-96-169).

EPA 1999a. "Data for Refining Anticipated Residue Estimates used in Dietary Risk Assessments for Organophosphate Pesticide;" draft document. March 26, 1999. http://www.epa.gov/fedrgstr/EPA-PEST/1999/April/Day-07/6033.pdf (64 FR 16967).

EPA 1999b. "Guidance for the Conduct of Bridging Studies for Use in Acute Dietary Probabilistic Risk Assessment;" draft document. July 29, 1999. http://www.epa.gov/fedrgstr/EPA-PEST/1999/August/Day-04/p20042.htm (64 FR 42372).

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EPA 1999f. “The Role of the Use-Related Information in Pesticide Risk Assessment and Risk Management;" draft document. June 29, 1999. http://www.epa.gov/fedrgstr/EPA-PEST/1999/July/Day-14/p17318.htm (64 FR 37977).

EPA 1999g. Memorandum from Margaret Stasikowski, Director Health Effects Division to Health Effects Division Staff. “Translation of Monitoring Data. HED Standard Operating Procedure 99.3 (3/26/99);” March 26, 1999.

EPA 1999h. “Use of the Pesticide Data Program (PDP) in Acute Risk Assessment;” draft document. May 5, 1999. http://www.epa.gov/fedrgstr/EPA-PEST/1999/May/Day-26/p13034.htm (64 FR 28485).

EPA 2000a. Background Document for the March 1, 2000 Meeting of the FIFRA Scientific Advisory Panel. “Office of Pesticide Programs' Comparison of Allender, RDFgen, and MaxLIP Decomposition Procedures;” February 1, 2000. http://www.epa.gov/scipoly/sap/index.htm

IV LIST OF COMMENTERS

Because of significant overlap in the individuals and organizations that commented on all three papers, EPA has chosen to combine the list of commenters. The draft paper entitled, "Data for Refining Anticipated Residue Estimates Used in Dietary Risk Assessments for Organophosphate Pesticides" was identified by Docket Control Number OPP-00591 and the two draft Guidance documents were identified by Docket Control Number OPP-00616.

Commenter [docket]	Affiliation
Arthur L. Craigmill, Ph.D., DABT, Extension Toxicology Specialist, *et al.* Michael A. Kamrin, Ph.D. Professor and Coordinator of Education and Outreach Programs [02/OPP-00591]	EXTOXNET Institute for Environmental Toxicology
Charles S. Baer, Ph.D. Registration and Regulatory Affairs [03/OPP-00591and 03/OPP-00616]	DuPont Agricultural Products
Dave Whitacre Vice President, Science [04/OPP-00591]	Novartis Crop Protection
Jacqueline Hamilton Senior Project Attorney	Natural Resources Defense Council
David B. Weinberg Attorney, Howrey & Simon	on behalf of: Makhteshim Agan of North America, Inc.
John Abbots [07/OPP-0059]	private citizen
Mark Maslyn Chairman [08/OPP-00591and L004/OPP-00616]	FQPA Implementation Working Group (IWG)
William Patrick Cockrell, Director Agricultural Policy [09/OPP-00591]	Florida Farm Bureau Federation (Part of IWG)

Commenter [docket]	Affiliation
Frank Priestley, President [10/OPP-00591]	Idaho Farm Bureau Federation
Jacqueline Hamilton Senior Project Attorney [L001/OPP-00591]	Natural Resources Defense Council
Sam Moore, President [11/OPP- 00591]	Kentucky Farm Bureau Federation
Dave Whitacre, Senior Vice President, Science [OPP-00591 and L002/OPP-00616]	Novartis Crop Protection, Inc.
Jack Laurie, President	Michigan Farm Bureau
no name	Pennsylvania Farm Bureau
Paul H. Gosselin, Acting Chief Deputy Director [L001/OPP-00616	California Department of Pesticide Regulation
no name given [04/OPP-00616]	Novigen Sciences, Inc. Washington, DC
no name given [05/OPP-00616]	Zeneca Ag Products